CAR-T Combinations (in Lymphoma)

Bologna, 14 Sept 2024

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Conflicts of Interest

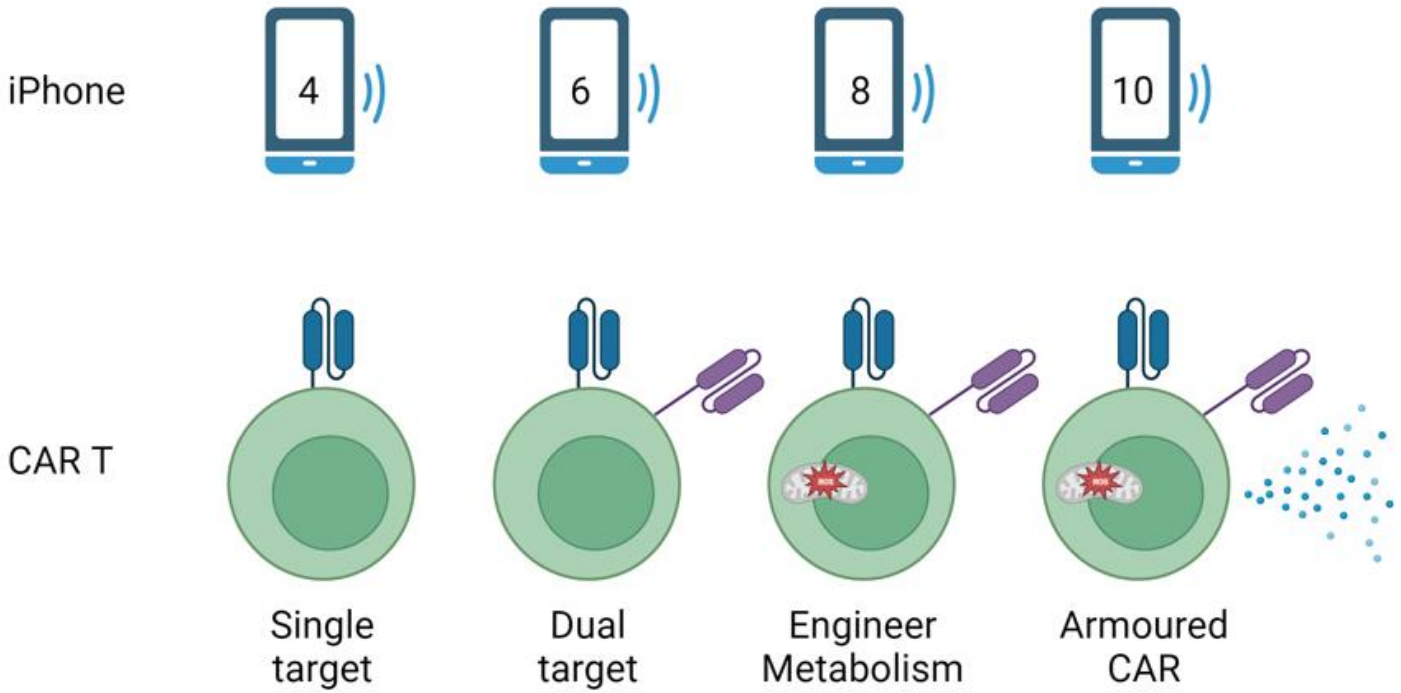
I have served on scientific advisory boards related to CAR T cell therapy for:

- Kite/Gilead, Novartis

I have institutional research funding from:

- Kite/Gilead, Incyte, Lilly

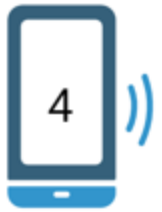
A problem in CAR T clinical development



Do you need to run a head:head trial to get approval?
Or do you have to test in post-CAR relapse?
Unclear regulatory path

A problem in CAR T clinical development?

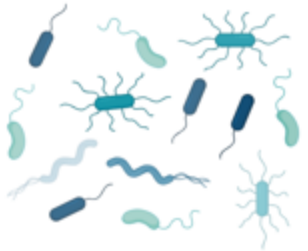
iPhone
+ other
gadgets

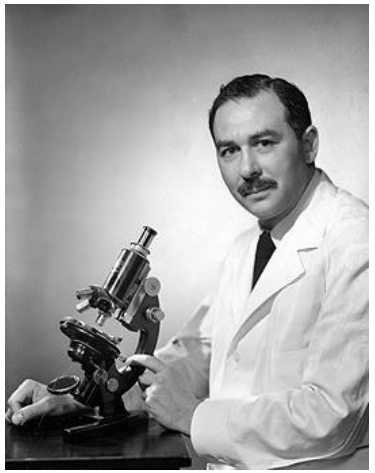




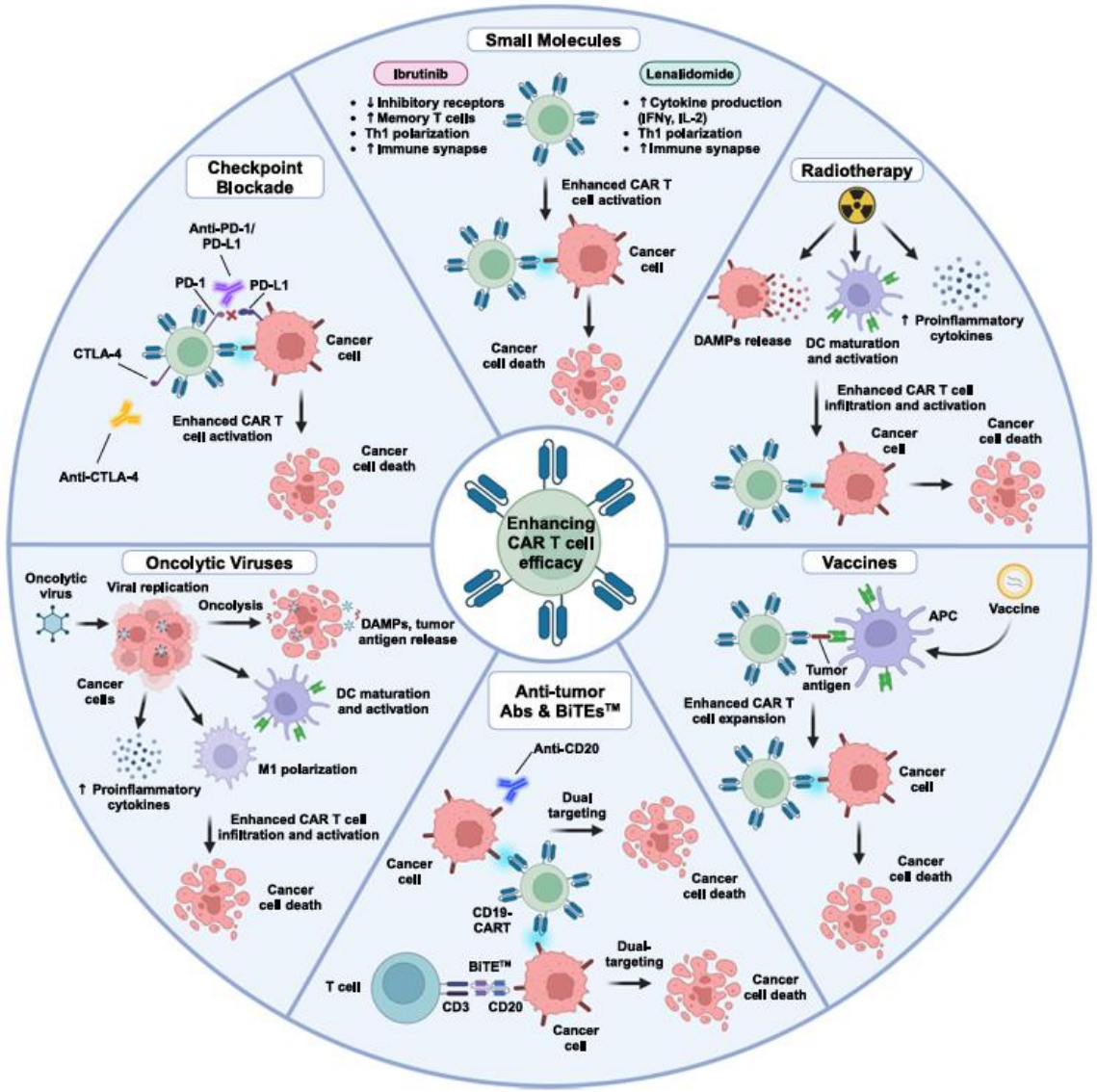
CAR T + other
interventions





Strategies for CAR T cell Combinations



Uslu, Castelli, and June Cancer Cell 2024

Strategies for CAR T cell Combinations

Table 1. Examples of currently active and recruiting clinical trials testing different agents to enhance efficacy of chimeric antigen receptor (CAR) T cells (ClinicalTrials.gov as of April 11th, 2024)

ClinicalTrials.gov identifier	CAR target	Combination agent	Combination agent function	Cancer type
1. NCT04134325 2. NCT05659628 3. NCT04995003 4. NCT05310591	1. CD30 2. CD19 3. HER2 4. CD19	1. Pembro/nivolumab 2. Tislelizumab 3. Pembro/nivolumab 4. Nivolumab	PD-1 antibody	1. r/r cHL 2. r/r DLBCL 3. Sarcoma 4. B-ALL
NCT04003649	IL13Ra2	Ipilimumab, nivolumab	CTLA-4 antibody, PD-1 antibody	Glioblastoma
NCT05052528	CD19	Rituximab	CD20 antibody	r/r DLBCL
NCT05495464	CD19	Acalabrutinib, rituximab	BTK inhibition, CD20 antibody	MCL
NCT04889716	CD19	Obinutuzumab, glofitamab, mosunetuzumab	CD20 antibody, CD3/CD20 BiTE, CD3/CD20 BiTE	r/r DLBCL
1. NCT05260957 2. NCT05633615 3. NCT05660369	1. + 2. CD19 3. EGFRvIII	1. + 2. Mosunetuzumab, polatuzumab vedotin 3. T cell engaging ab	1. + 2. CD3/CD20 BiTE, CD79b antibody 3. EGFR/CD3 BiTE	1. r/r NHL 2. r/r DLBCL, FL 3. Glioblastoma
1. NCT03960840 2. NCT05744037 3. NCT05020392 4. NCT04257578 5. NCT04484012 6. NCT05202782 7. NCT05873712	CD19	1. Ibrutinib 2. Ibrutinib 3. Not specified 4. Acalabrutinib 5. Acalabrutinib 6. Zanubrutinib 7. Zanubrutinib	BTK inhibition	1. CLL, SLL 2. r/r NHL 3. r/r B cell lymphoma 4. B cell lymphoma 5. r/r MCL 6. B-NHL 7. Richter's transform.
NCT05672173	CD19	Nivolumab, ibrutinib	PD1 antibody, BTK inhibitor	Richter's transform.
NCT06045806	BCMA	Lenalidomide	Thalidomide derivate	MM
1. NCT05801913 2. NCT05432635 3. NCT04503278 4. NCT05381662 5. NCT03291444	1. CMV-CD19 2. CMV-CD19 3. CLDN6 4. CD19 5. CD33	1. CMV-MVA Triplex 2. CMV-MVA Triplex 3. RNA-LPX 4. CD19 feeder T cells 5. Dendritic cells	Vaccine	1. B-NHL 2. B-NHL 3. CLDN6+ solid tum. 4. ALL 5. AML/MDS
1. NCT03740256 2. NCT05057715	1. HER2 2. Mesothelin	1. CAdVEC 2. VCN-01	Oncolytic virus	1. HER2+ solid tum. 2. Pancreatic cancer, ovarian cancer
1. NCT05800405 2. NCT06104592 3. NCT05621096 4. NCT04790747 5. NCT05574114 6. NCT05805371 7. NCT05514327 8. NCT06043323 9. NCT04601831 10. NCT05336383	1. CD19 2. CD19 3. CD19 4. n/s 5. CD19 6. PSCA 7. CD19 8. CD19 9. CD19 10. BCMA	Radiotherapy		1. r/r LBCL 2. r/r LBCL 3. r/r B-NHL 4. r/r hematol. malig. 5. B cell lymphoma 6. Prostate cancer 7. r/r DLBCL 8. r/r FL 9. r/r NHL 10. r/r MM

Uslu, Castelli, and June Cancer Cell 2024

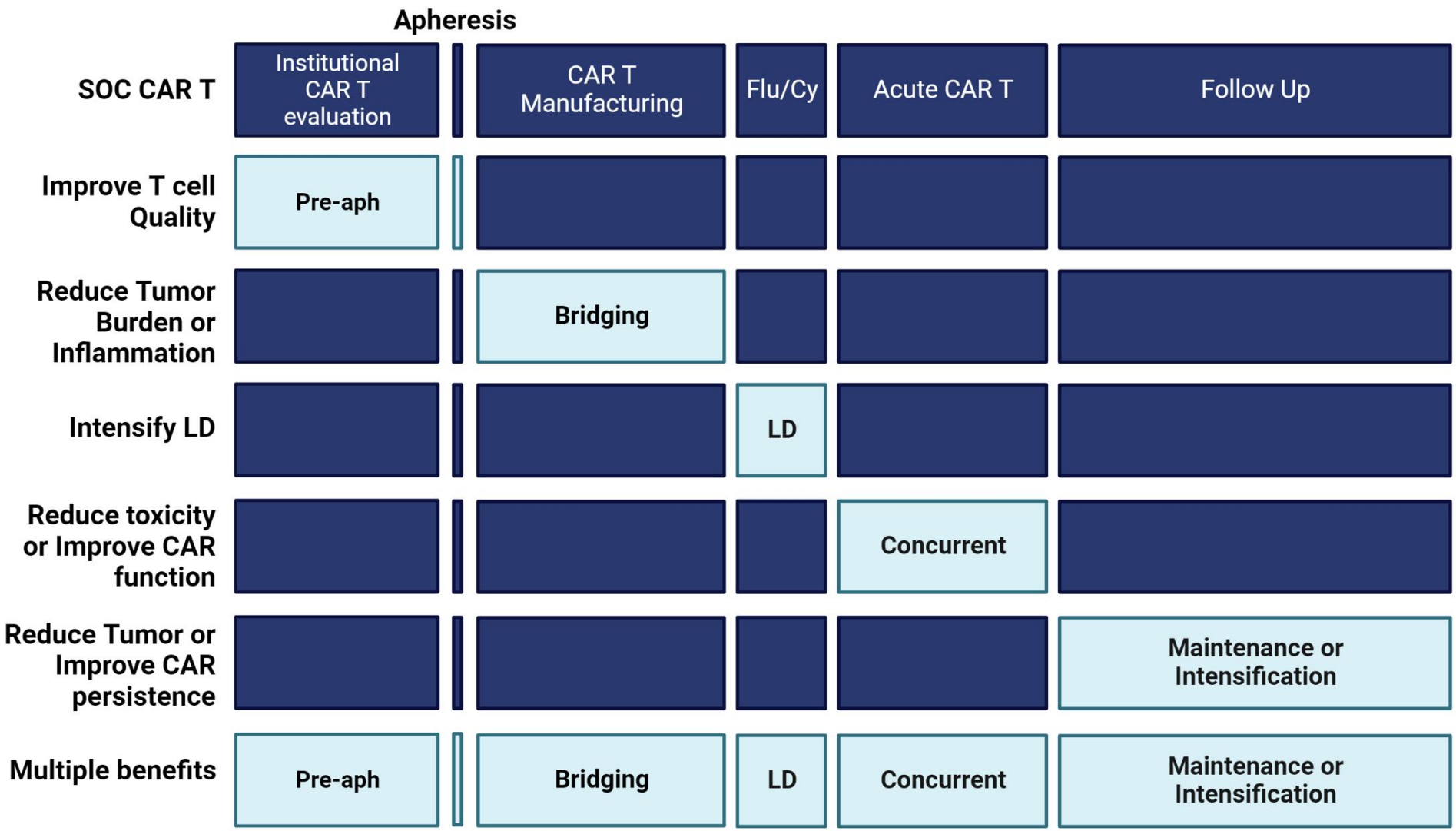
Moffitt IITs Currently Enrolling Combinations

NCT06104592 – Comprehensive Ablative Bridging Irradiation Prior to CAR T in R/R DLBCL

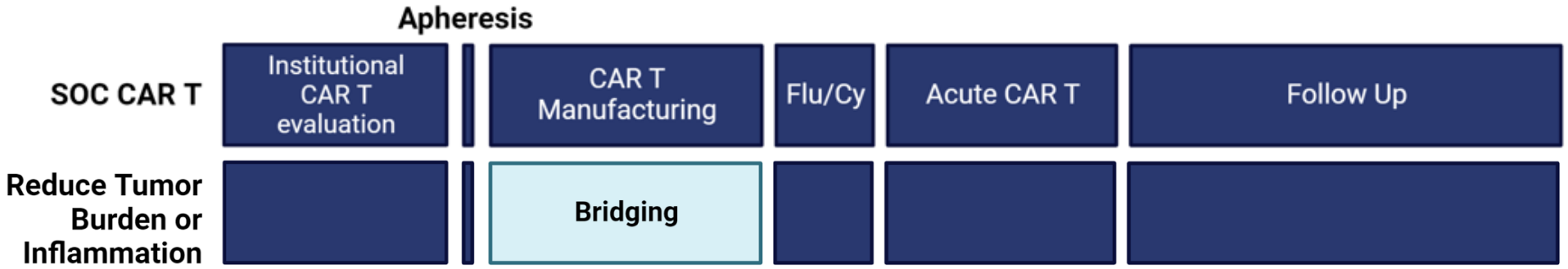
NCT05757219 – Itacitinib Pre-modulation in DLBCL Receiving CAR T cell therapy

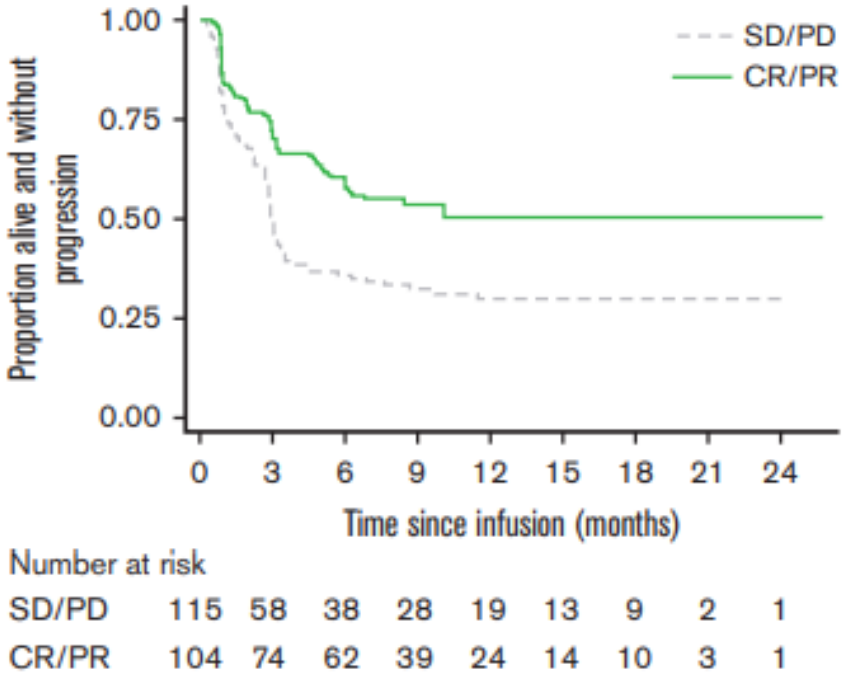
NCT06553872 – Phase 2 Open Label Randomized Study of Pirtobrutinib and Brexucabtagene Autoleucel in R/R Mantle Cell Lymphoma

Goals of Combinations with CAR T cell therapies



Combinations Aimed at Improving Bridging





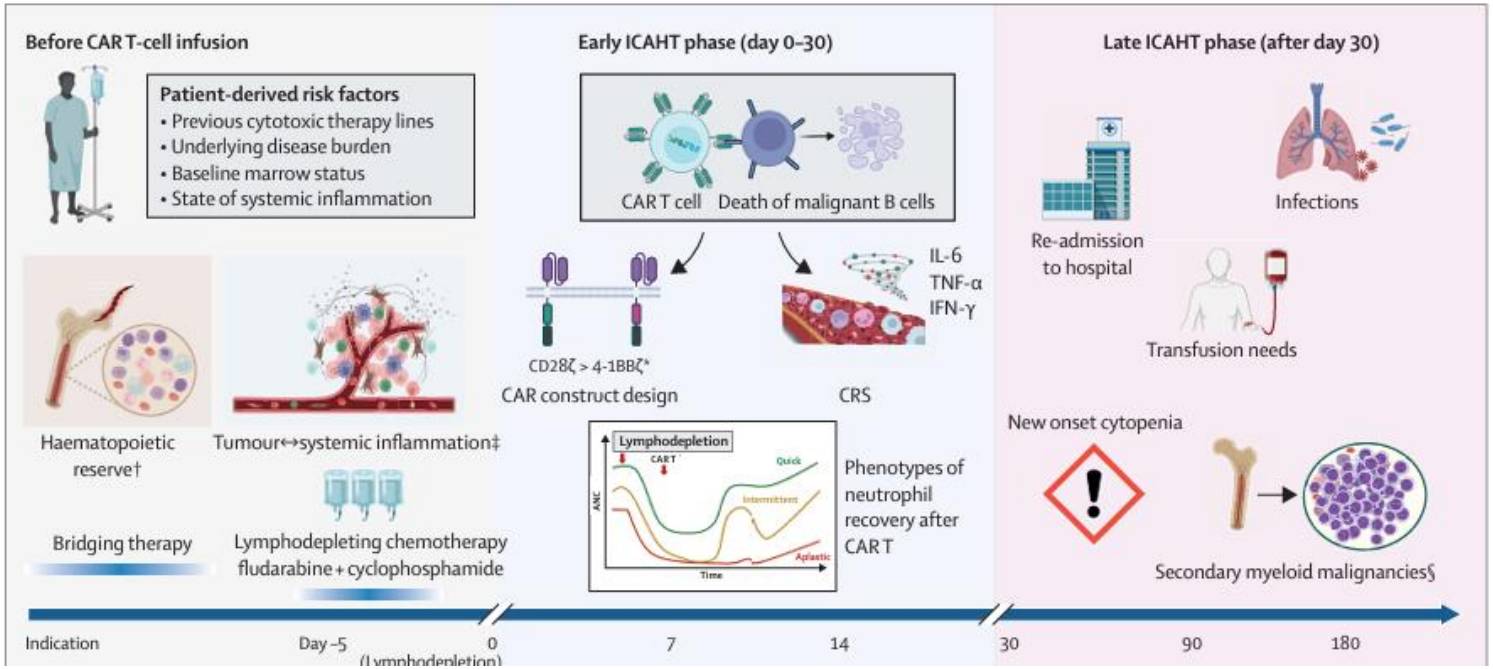
Roddie et al. Blood Adv. 2023

Response to bridging associates with improved outcomes after CAR T.

Possible effects of improved bridging:

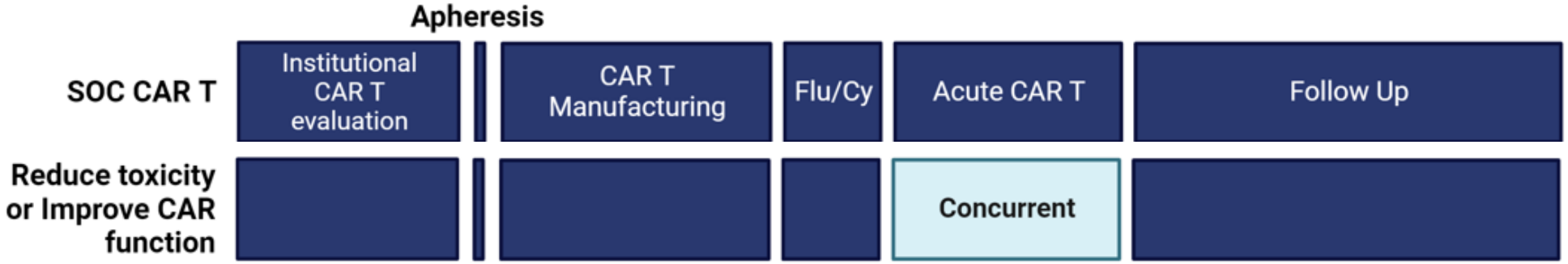
- Reduce tumor burden
- Reduce systemic inflammation (CRP/ferritin/IL-6)
- Improve tumor microenvironment

Combinations Aimed at Improving Lymphodepletion



Rejeski et al. Lancet Hematol. 2024

Combinations Aimed at Reducing Toxicity

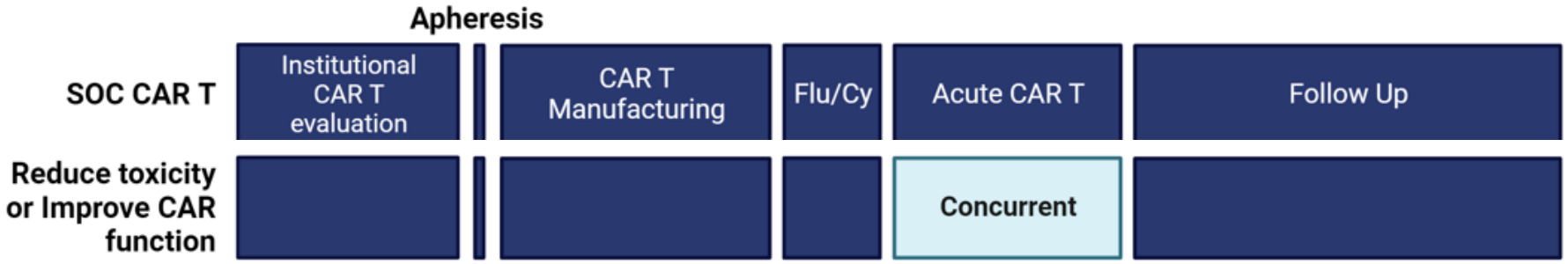


Examples of trials giving concurrent therapies to reduce CAR T cell toxicity:

- Prophylactic anti-cytokines:
  - Steroids
  - Tocilizumab (anti-IL6)
  - Anakinra (anti-IL1)
  - Lenzilumab (anti-GM-CSF)
  - Emapalumab (anti-IFN-gamma)

- Concurrent JAK1 inhibition: Itacitinib

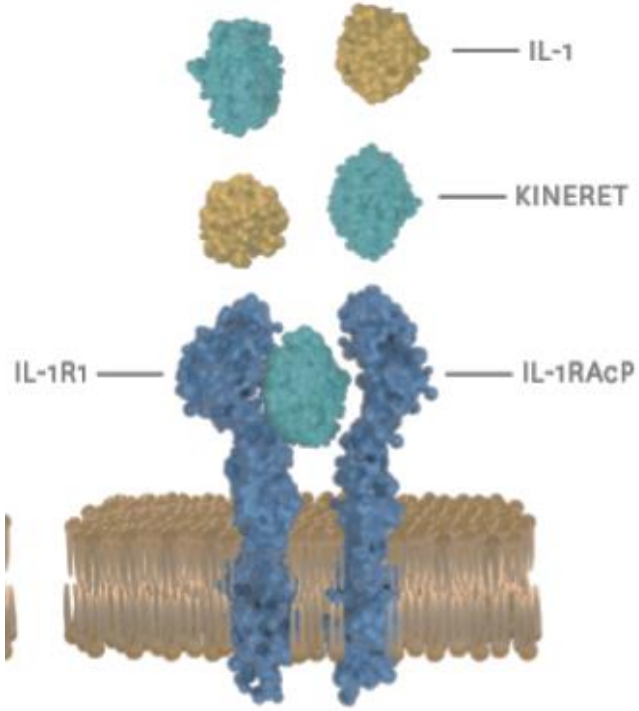
Combinations Aimed at Reducing Toxicity



Prophylactic Anakinra 100 mg BID sc
N=31 (n=23 axi-cel/DLBCL; n=4 brexu-cel/MCL; n=4 tisa-cel)

Started either at Day 2 (n=25), or if fever before Day 2 (n=6)
- Continued until at least Day 10.

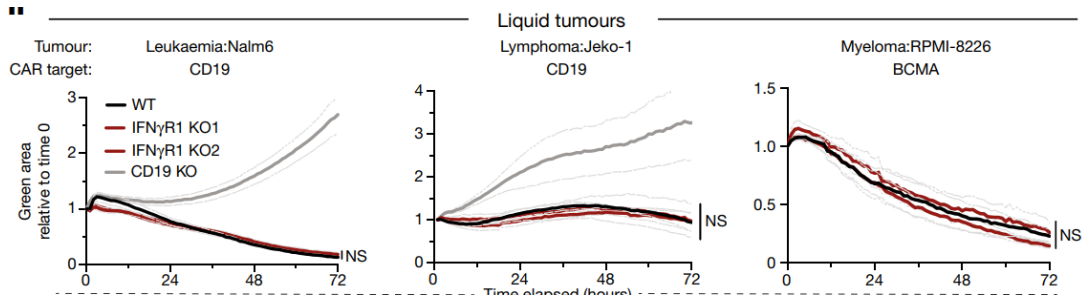
All-grade ICANS 19%, severe ICANS 9.7% (none grade 4 or 5).
All-grade CRS 74%, severe CRS 6.4%.
ORR 77%, CR 65%.



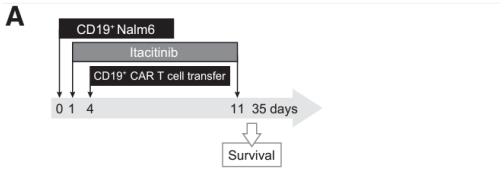
Park et al. (MSK) Nat. Med. 2023

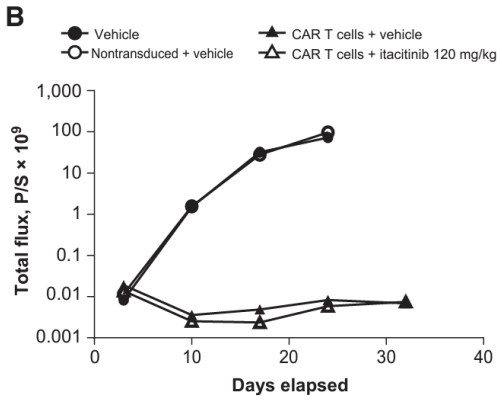
Similar studies by Strati et al. (MD Anderson) Blood Adv. 2023 and Frigault et al. (MGH) ASH 2021

Combinations Aimed at Reducing Toxicity



Liquid tumors do not require IFN/JAK1/2 signaling for CAR cytotoxicity (Jensen et al. Nature 2022)





Itacitinib, a JAK1 inhibitor, does not affect CAR T cell efficacy in mice (Huarte et al. Clin. Cancer Res. 2020)

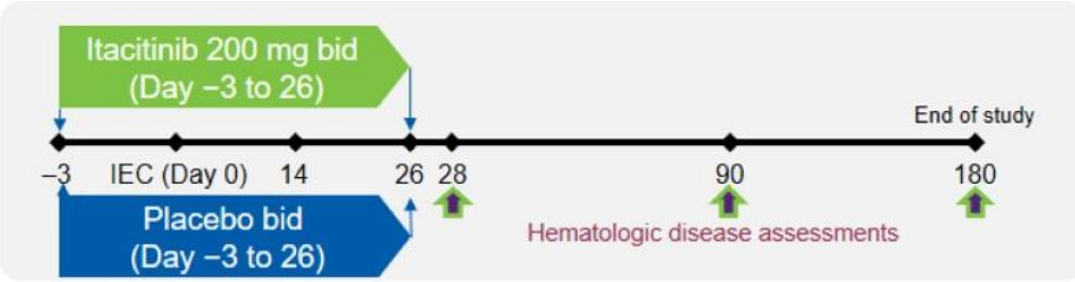
Combinations Aimed at Reducing Toxicity

PART 2

Main eligibility criteria

- Age ≥18
- Eligible for treatment with axicabtagene ciloleucel
- ECOG 0 or 1

N=46 patients (23 patients/arm)

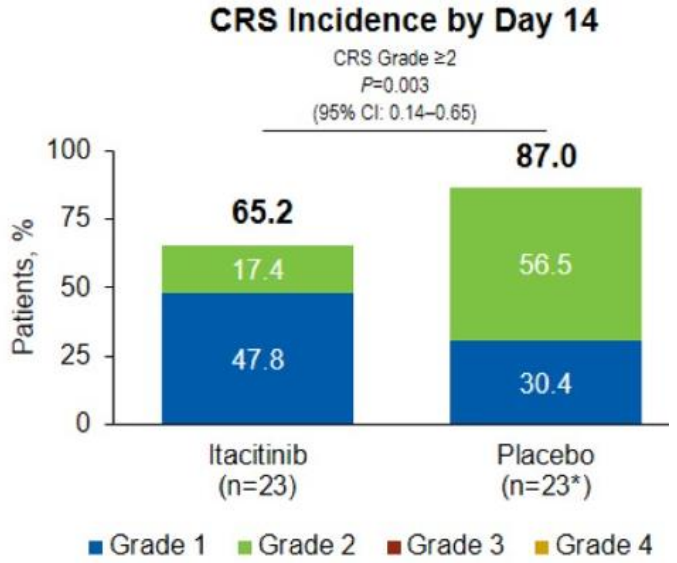


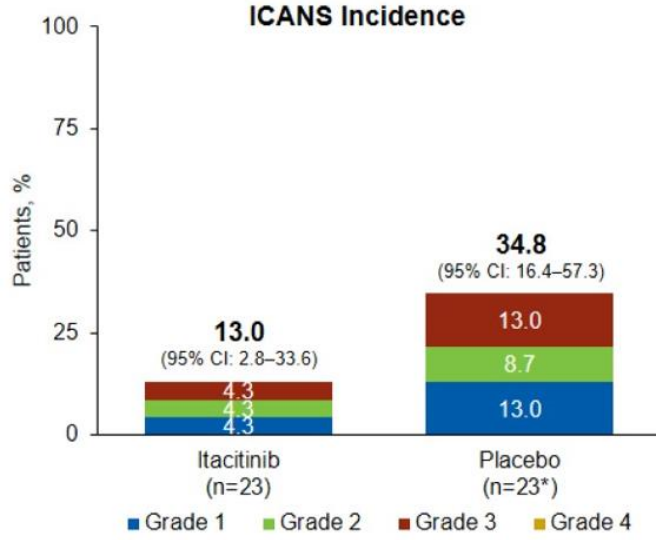
Tocilizumab could be given for CRS grade 1 if no improvement was observed within 72 hours

- **Primary endpoint**: Incidence of CRS grade ≥2 by Day 14 per ASTCT consensus grading

Frigault et al. ASH 2023

Combinations Aimed at Reducing Toxicity

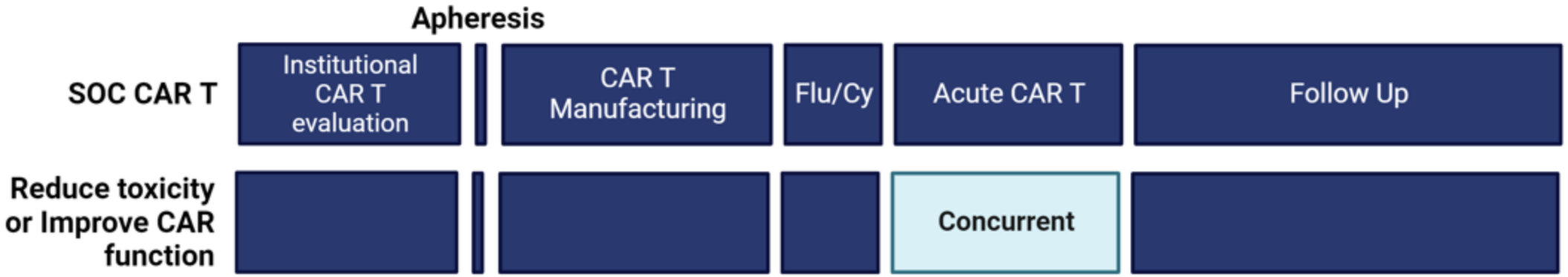




	Itacitinib + axi-cel	Placebo + axi-cel
ORR at 6 months,† n (%)	**9 (39.1)**	**6 (26.1)**
[95% CI]	[19.7, 61.5]	[10.2, 48.4]
CR	9 (39.1)	5 (21.7)

Frigault et al. ASH 2023

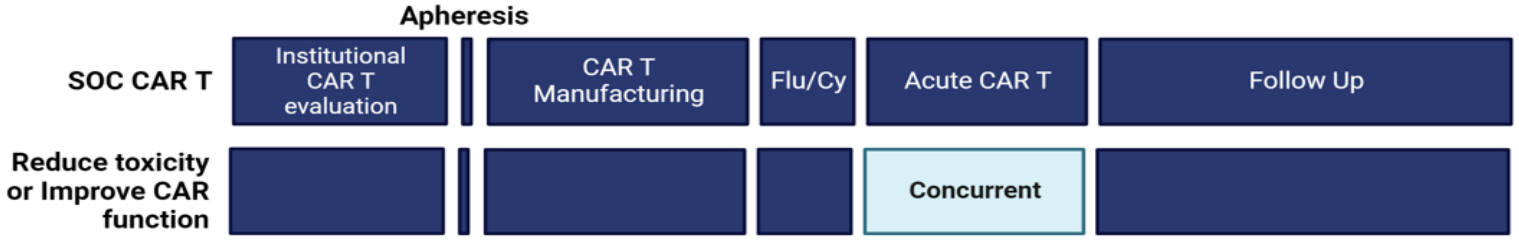
Combinations Aimed at Increasing CAR Function



Examples of trials giving concurrent therapies to increase CAR T cell function:

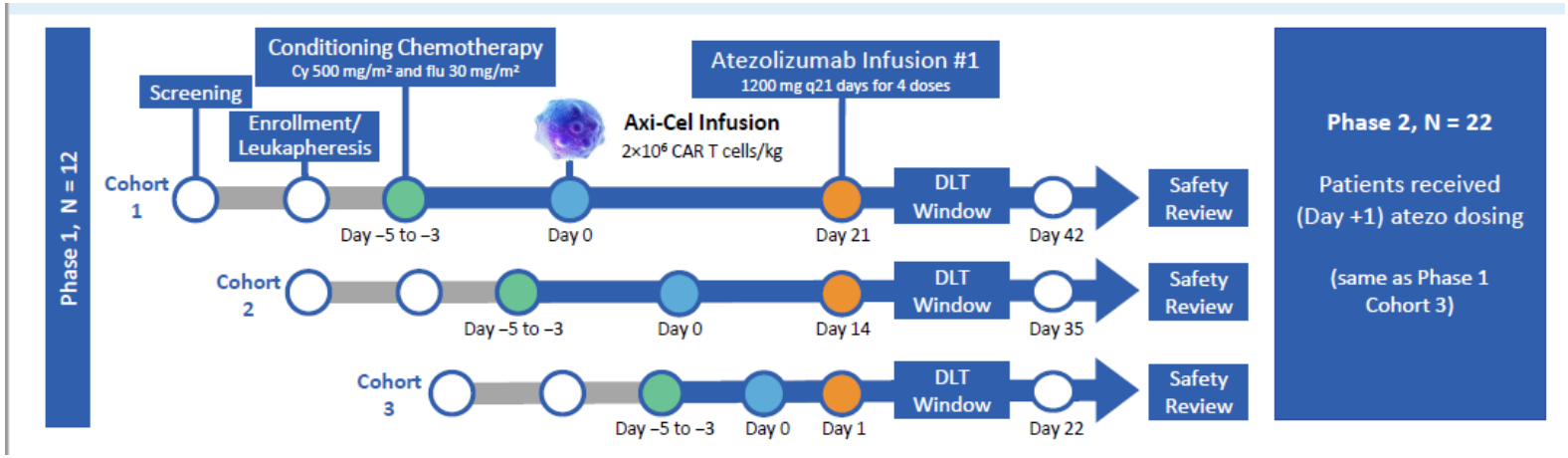
- CAR T plus immune modulators: Anti-PD-L1; 4-1BB agonist

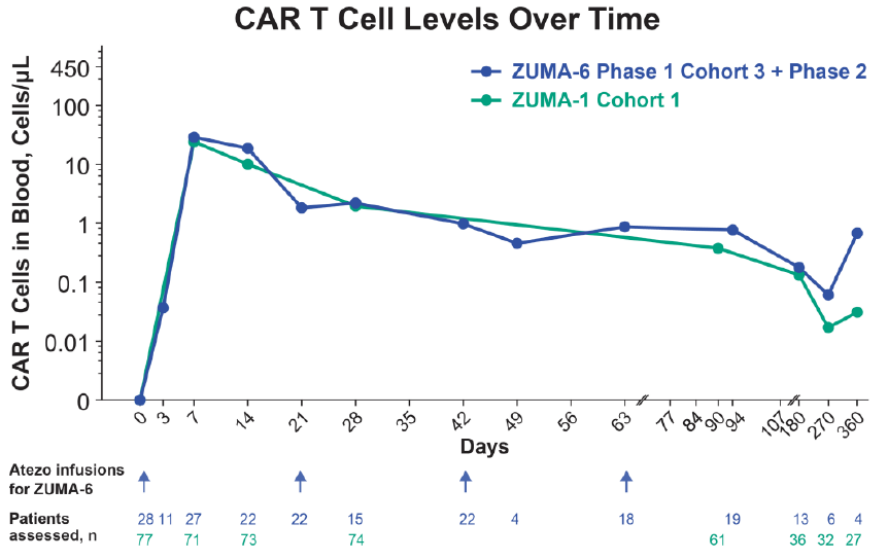
Combinations Aimed at Increasing CAR Function



Atezolizumab (anti-PD-L1) plus axi-cel (CD19/CD28) in R/R DLBCL (ZUMA-6)

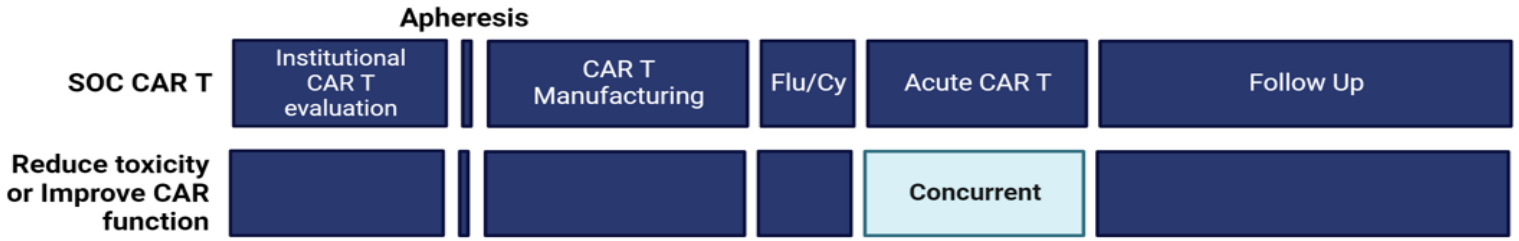
N=28. ORR 75%, CR 46%, Gr3+ CRS 4%, Gr3+ ICANS 8%





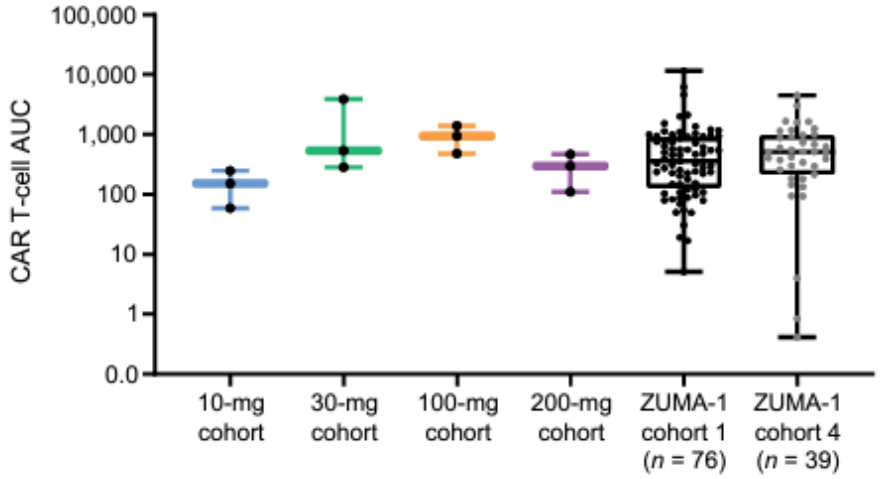
Jacobson et al. AACR 2020

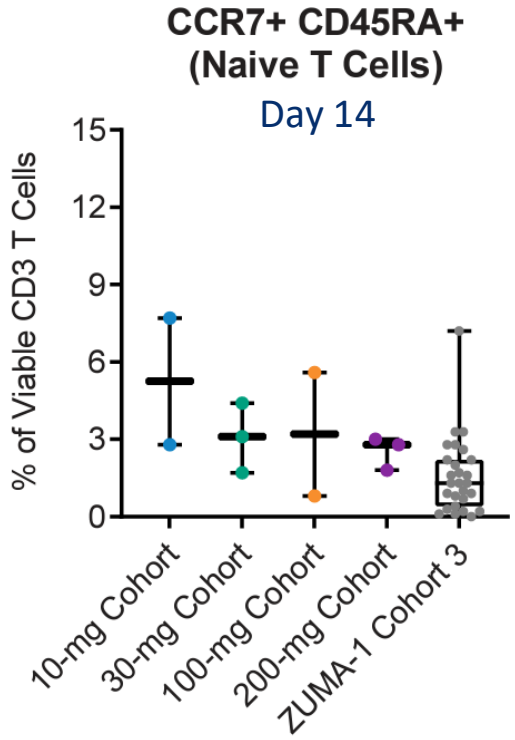
Combinations Aimed at Increasing CAR Function

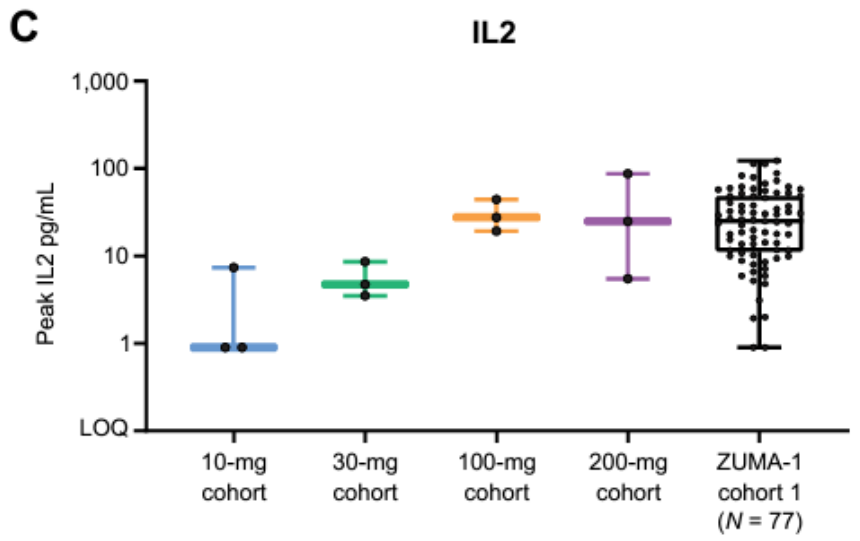


Utomilumab (4-1BB agonist) plus axi-cel (CD19/CD28) in R/R DLBCL (ZUMA-11)

N=12. ORR 75%, CR 58%, no Gr3 CRS or Gr3 ICANS

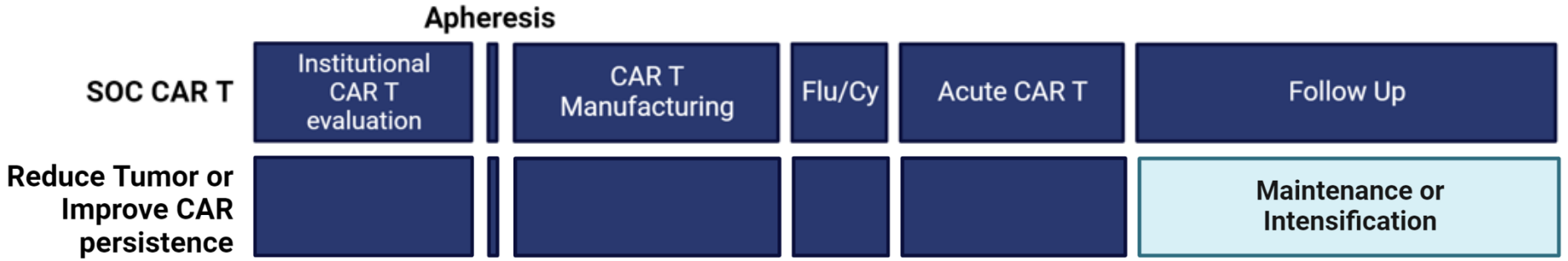






Jain et al. Clin. Cancer Res. 2023

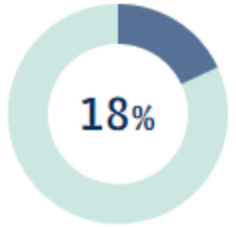
Combinations as Maintenance/Intensification



SWOG S2114: A Randomized Phase II trial of consolidation therapy following CD19 CAR T-cell treatment for Relapsed/Refractory Large B-cell Lymphoma or Grade IIIB Follicular Lymphoma

Day 30 PET – if SD or PR →

1. **CD79b ADC (Pola)**
2. **CD20/CD3 bispecific (Mosun)**
3. **Mosun+Pola**
4. **None**

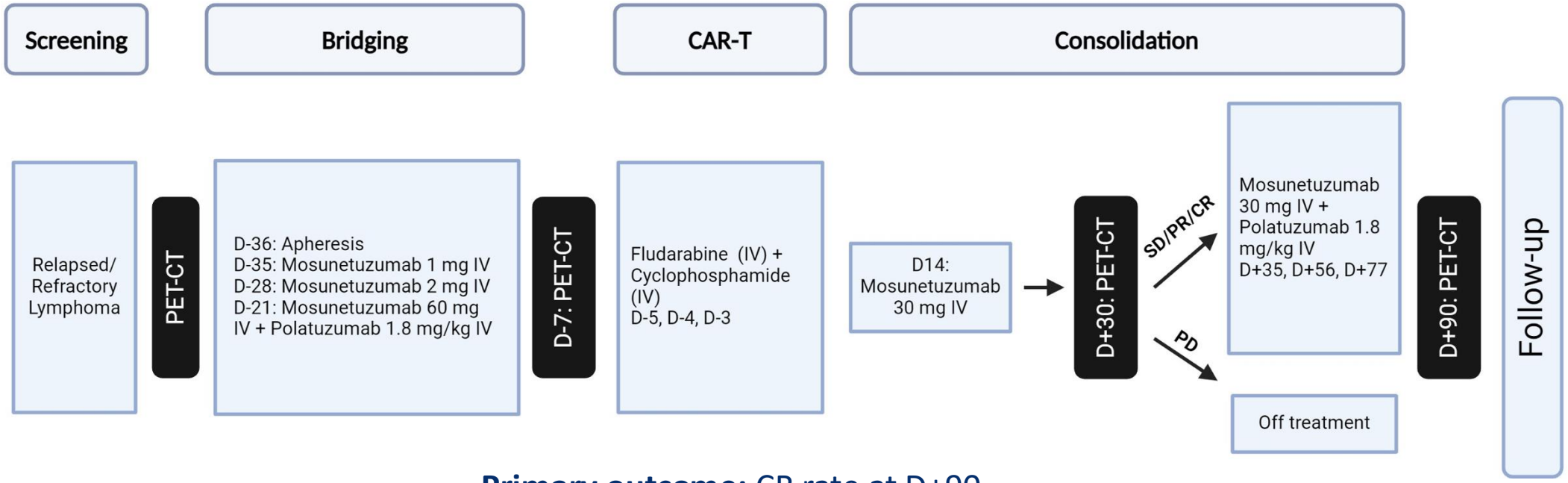


Accrual

Opened Feb 2023

Combinations with Multiple Benefits

Mosun (CD20/CD3 bispecific), Polatuzumab (CD79 ADC), and CAR T for R/R DLBCL

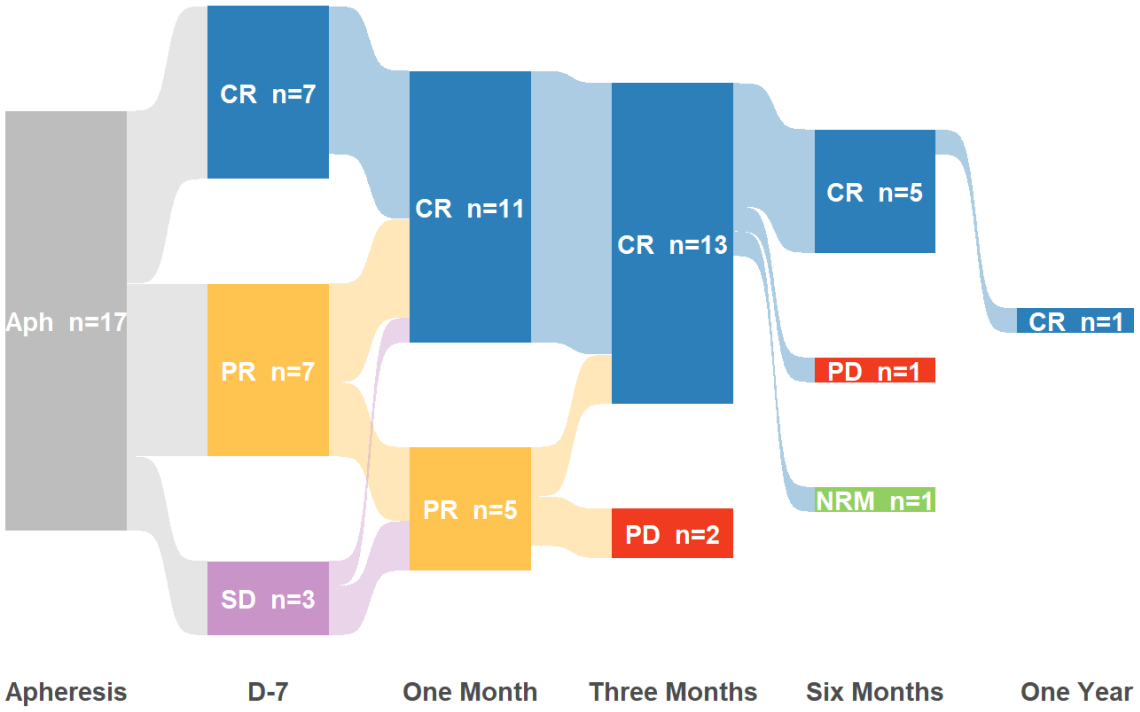


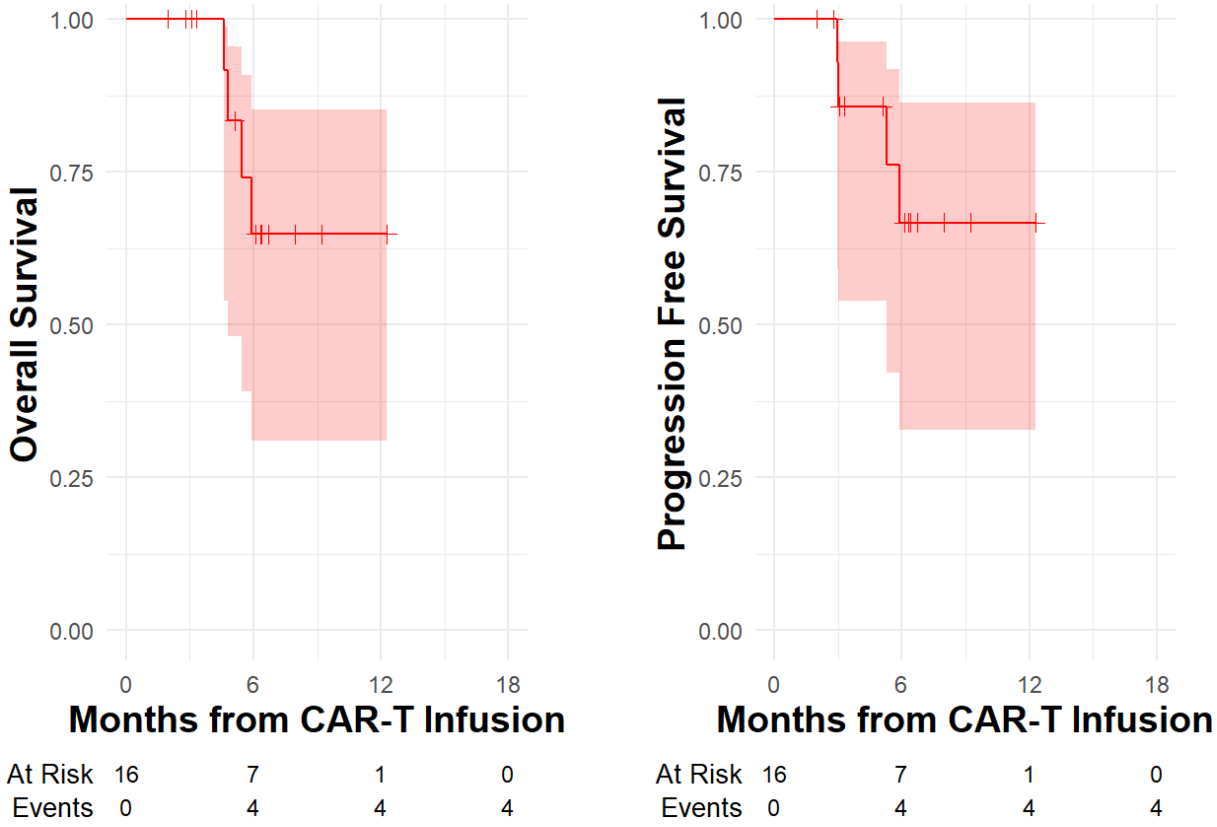
Primary outcome: CR rate at D+90
Secondary outcomes: PFS, OS, DOR

Spiegel, Lekakis et al. IWCART 2024

Combinations with Multiple Benefits

Mosun (CD20/CD3 bispecific), Polatuzumab (CD79 ADC), and CAR T for R/R DLBCL





CMV reactivation 59%; now managed with letermovir
Grade 3+ CRS: 0%
Grade 3+ ICANS: 31%

Median follow-up: 6.3 months
6-month PFS: 67%

Spiegel, Lekakis et al. IWCART 2024

Combinations with Multiple Benefits

CAR T-cells and Time-Limited Ibrutinib as Treatment for Relapsed/Refractory Mantle Cell Lymphoma: Phase II TARMAC Study Primary Analysis

TARMAC study

(NCT04234061)

Key inclusion criteria:

- Relapsed/refractory MCL
- ≥18yo
- Radiographically assessable or bone marrow phase disease

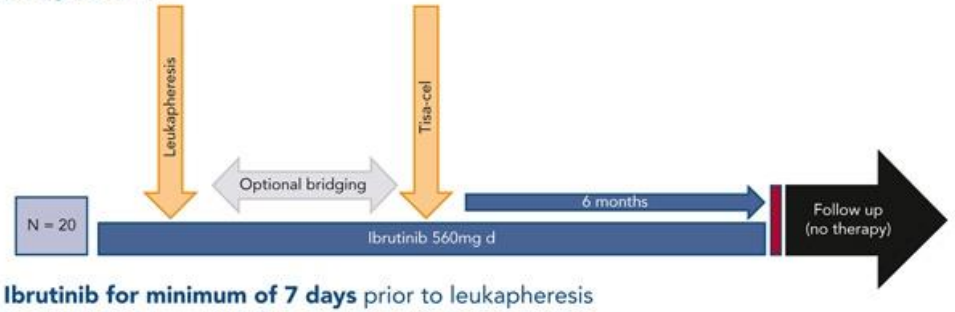
Key exclusion criteria:

- Prior allogeneic transplant
- Active CNS involvement

Genomic characteristics:

- 9 patients with *TP53* aberrancy
- 7 with concurrent deletion + mutation

Study Schema:



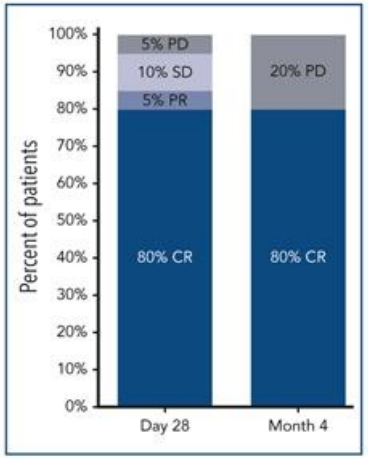
Ibrutinib for minimum of 7 days prior to leukapheresis
Lymphodepletion with fludarabine/cyclophosphamide x 3 days
Time-limited therapy: ibrutinib ceased at 6 months if measurable residual disease (MRD) negative by flow cytometry

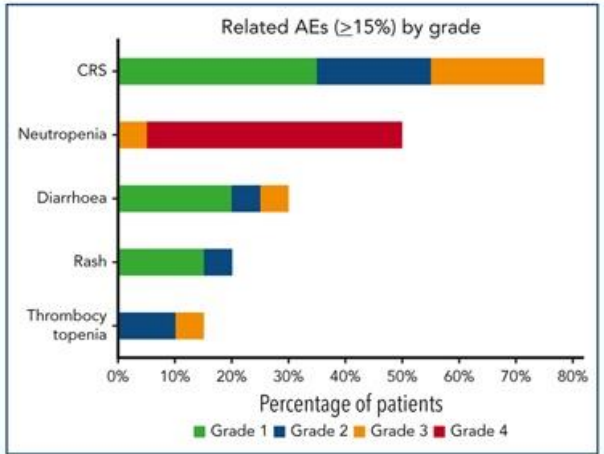
Main findings:

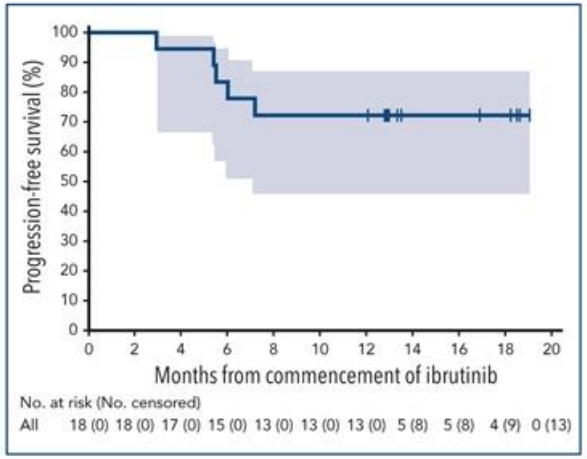
Response,

adverse events,

and PFS





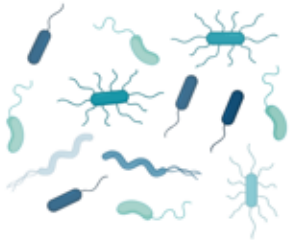


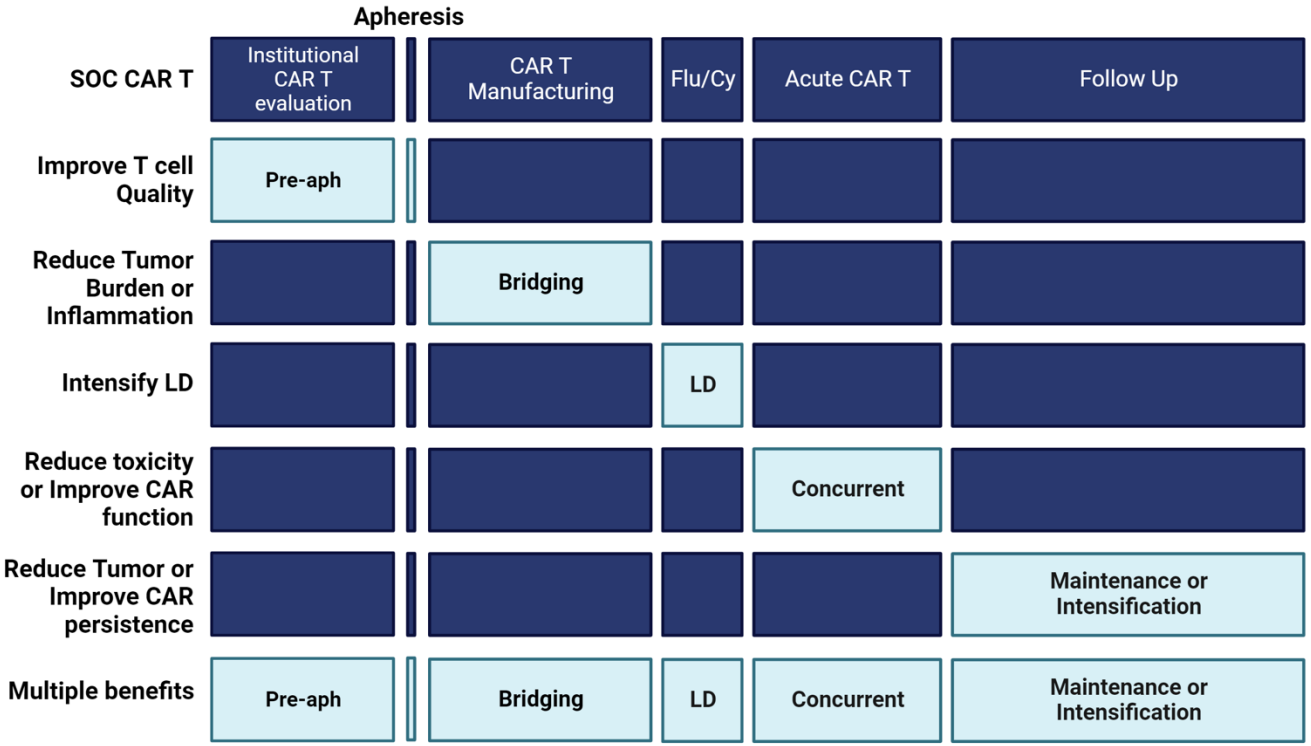
N=20 patients
Ibrutinib (BTKi) plus Tisa-cel
12 month PFS 75%
Grade 3+ CRS: 20%
Grade 3+ ICANS: 0%

Minson et al. Blood 2024

A solution for CAR T clinical problems?

CAR T + other interventions





CAR T Combinations:

- Many possibilities for combinations
- Timing of the combination may leverage different aspects of tumor and CAR T cell biology
- Potentially straightforward for clinical development

Moffitt Lymphoma CAR T cell Therapy

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Alex Lazaryan
Sameh Gaballa
Sayeef Mirza
Taiga Nishihori
Farhad Khimani